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Models for the description of angioscotomas

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Abstract

To describe small scotomas in visual field examinations several statistical models are proposed and applied to the evaluation of angioscotoma in 13 ophthalmologically normal subjects. A special perimetric grid is used where thresholds can be estimated along a line of narrow-spaced test points which crosses the predicted location of the retinal vessel. A two-stage analysis employs single estimations to fit a threshold curve by means of a special parametric description of the luminance difference sensitivity threshold as a function of stimulus position. An alternative model incorporates the threshold as a function of position into the probabilistic description of the binary response (stimulus seen/not seen). © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Angioscotomas are small and rather shallow scotomas caused by retinal vessels. Common visual field examinations using rather coarse grids are likely to overlook such scotomas. A good description of angioscotomas by automated perimetry needs both a special perimetric grid and a suitable statistical model to evaluate the responses given at test locations near the vessel. Such methods are also applicable to other small scotomas.

In the past, perimetric control of angioscotoma was believed to be a clinically important diagnostic procedure providing the examiner with additional information on glaucoma and intracranial pressure (Dashevsky, 1938; Weekers & Humblet, 1945; Welt, 1945; Goldmann, 1947; Abe, 1968).

In practice, visual field defects caused by retinal vessels are graded as physiologically induced nuisance effects. However, due to their minimal size, angioscotomas can additionally serve as quality control for spatially high resolution perimetry (Häberlin, Funkhouser & Fankhauser, 1983; Zulauf, 1988, 1990a,b; Safran, Halfon, Safran & Mermoud, 1995; Remky, Beausencourt & Elsner, 1996). This procedure should be of major importance for functional detection and follow-up of minute morphological retinal lesions, e.g. slit like nerve fiber layer defects, circumscribed processes of vascular as well as inflammatory origin. Of course, it has to be considered that there are differences in the reason of the above mentioned types of scotomas and angioscotomas, respectively. In the first case there is an impairment of the neuronal integrity and function of retinal elements, e.g. retinal ganglion cells whereas in the case of angioscotomas a masking of photoreceptors takes place.

Early reviews on angioscotoma are given by Evans (1938) and Dubois-Poulsen (1952). More recent results were contributed by Zulauf (1988, 1990a), who made a first attempt at a more exact quantification of angioscotoma. He used profile cuts with a point spacing of 0.2° and threshold estimations to quantify angioscotoma. Häberlin et al. (1983) applied the spatially adaptive program SAPRO in a study of angioscotoma. They found angioscotoma widths in 'the order of 0.6°' and angioscotoma depths up to 10 dB. Using SLO microperimetry, Remky et al. (1996) detected comparatively small scotoma depths (0.1–5 dB).

Given some threshold estimations across a line of test points crossing a vessel perpendicularly, luminance difference sensitivity threshold (lds-threshold) as a func-

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tion of test point location can be fitted to an appropriate function using e.g. least squares regression. This function should describe the angioscotoma as exact as possible. The parameters of this function should present scotoma width, depth and location. Nevertheless, threshold estimations for the single test points are rather uncertain when only a few stimulus presentations are employed. A better description would be based on a probabilistic model using all responses simultaneously and including directly the lds-threshold as a function of stimulus position.

2. Models and statistical methods

Based on a digitised fundus image, a line of closely spaced test points which crosses an isolated vessel nearly perpendicularly can be incorporated into a perimetric grid (fundus oriented perimetry, see Schiefer, Stercken-Sorrenti, Dietrich, Friedrich & Benda, 1996). As an example, Fig. 1 shows the perimetric grid used for one subject (subject 6). The grids for the subjects differ only in the test point line crossing the vessel.

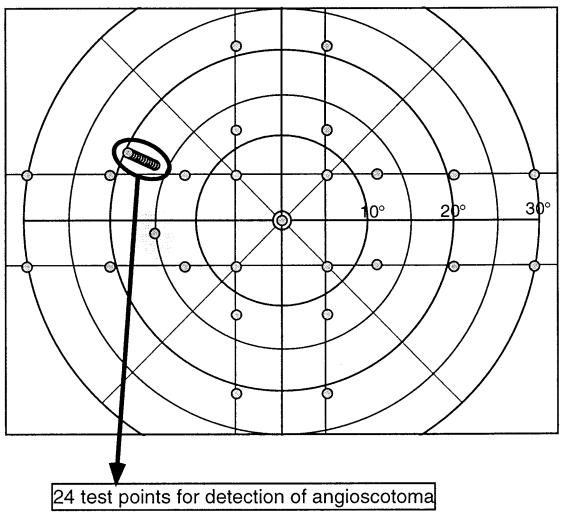

Fig. 1. Perimetric grid for subject 6.

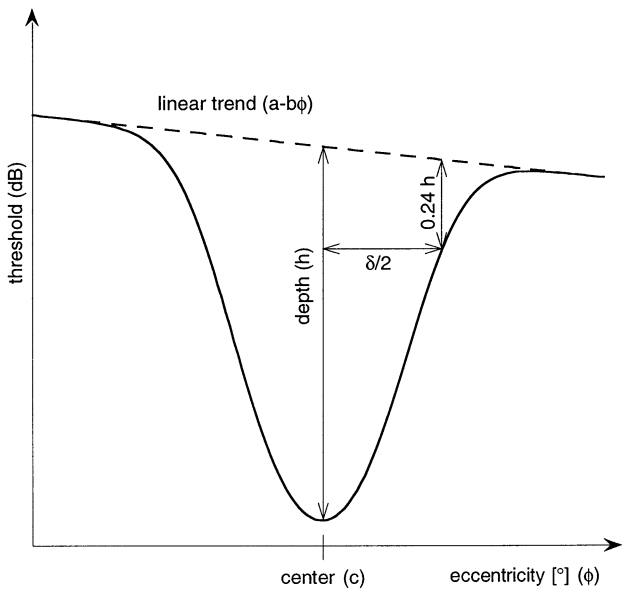

Fig. 2. Model for angioscotomas.

Table 1
Estimated angioscotoma width and depth for 12 ophthalmologically normal subjects

Subject	Width (°) (δ)		Depth (dB) (h)	
	One-stage	Two-stage	One-stage	Two-stage
1	0.76	0.72	3.9	3.6
2	0.93	0.94	2.5	2.4
3	1.92	1.86	6.4	5.8
4	0.37	0.41	3.6	3.8
5	0.70	0.71	6.8	6.5
6	0.99	1.10	3.8	3.5
7	2.02	1.94	2.6	3.1
8	0.24	0.23	2.7	2.9
9	1.03	1.12	3.7	4.0
10	1.32	1.37	3.3	3.3
11	1.45	1.44	1.9	1.7
13	0.12	0.11	7.6	8.8

2.1. Parametrization of the threshold course

If ϕ measures the distance from a test point on a line crossing a retinal vessel to a fixed point of reference on this line, the threshold should be described by a suitable parametric function $\mu_\theta(\phi)$ including the parameters scotoma depth, width and position. Adding a linear trend of the threshold near the vessel and besides the scotoma, threshold course can be depicted by

$$\mu_\theta(\phi) = a - b\phi + h\left(\tanh\left[\left(\frac{\phi - c}{\delta/2}\right)^2\right] - 1\right) \quad (1)$$

where $\theta = (a,\ b,\ h,\ c,\ \delta)$. The straight line $a - b\phi$ describes the linear trend of the threshold near the vessel and beside the scotoma, c the center of angioscotoma and h the scotoma depth at the center. Parameter δ represents a measure of scotoma width (see Fig. 2). Instead of using the hyperbolic tangents a Gaussian-like function could be employed:

$$\mu_\theta(\phi) = a - b\phi - h\ \exp\left[-\left(\frac{\phi - c}{\tilde{\delta}/2}\right)^2\right]. \quad (2)$$

The parameters for the linear trend, scotoma depth and position a, b, h, c are comparable in both models, whereas interpretation of scotoma width depends on the model choice.

When no scotoma is present the corresponding threshold course would be

$$\mu_\theta(\phi) = a - b\phi \quad (3)$$

If the line of test points corresponds to one meridian of the visual field the distance ϕ can be set to the eccentricity of the test point. This was the case for the examinations we made.

2.2. One-stage and two-stage analysis

Common models for the response probability of the experimental subject, i.e. for the psychometric function, are logistic ('logit') and probabilistic ('probit') regression models (Treutwein, 1995). For most purposes, the two models agree very closely (see Cox & Snell, 1989). This article employs the logit-model, though the probit-model renders very similar outcomes.

Consider an examination at test point distances (eccentricities) $\phi_1 \ldots \phi_k$ resulting in threshold estimations $\hat{\mu}(\phi_1) \ldots \hat{\mu}(\phi_k)$. We obtained these single estimates by maximum likelihood using a logistic regression model. Nonetheless, other estimation methods could be employed.

A two-stage analysis uses these estimates to fit an appropriate function like $\mu(\phi)$ (e.g.) by least squares estimation, i.e. it solves

$$\sum_{i=1}^{k} (\hat{\mu}(\phi_i) - \mu_\theta(\phi_i))^2 \stackrel{!}{=} \min_\theta. \quad (4)$$

Two-stage fitting can be calculated by standard programs for data analysis. Nevertheless, it does not consider differences in the precision of the single estimates, which may yield misleading results.

One-stage fitting, on the other hand, is based on a model where the probability of stimulus perception depends on stimulus intensity and test point location. Let x_{ij} be the i-th stimulus intensity measured in dB at test location ϕ_j and Y_{ij} the corresponding response variable with $Y_{ij} = 1$ if the stimulus was seen and $Y_{ij} = 0$ otherwise. Furthermore let n_j be the number of stimuli presented at test location ϕ_j. Using a logistic (logit) model for the binary response, the probability of a seen

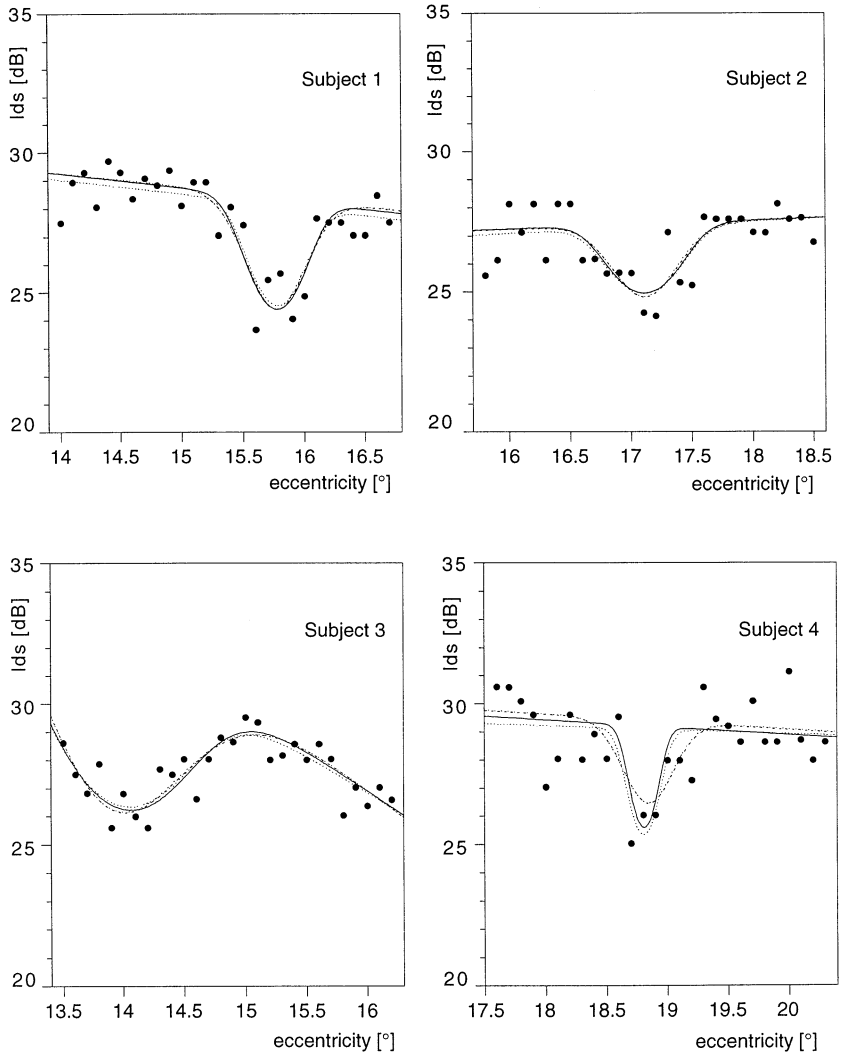

Fig. 3. Angioscotoma estimation for 13 ophthalmologically normal subjects. Points represents single threshold estimates. —, One-stage fitting using hyperbolic tangents model. -·-·-·, One-stage fitting using Gaussian-like tangents model. ···, Two-stage fitting using hyperbolic tangents model.

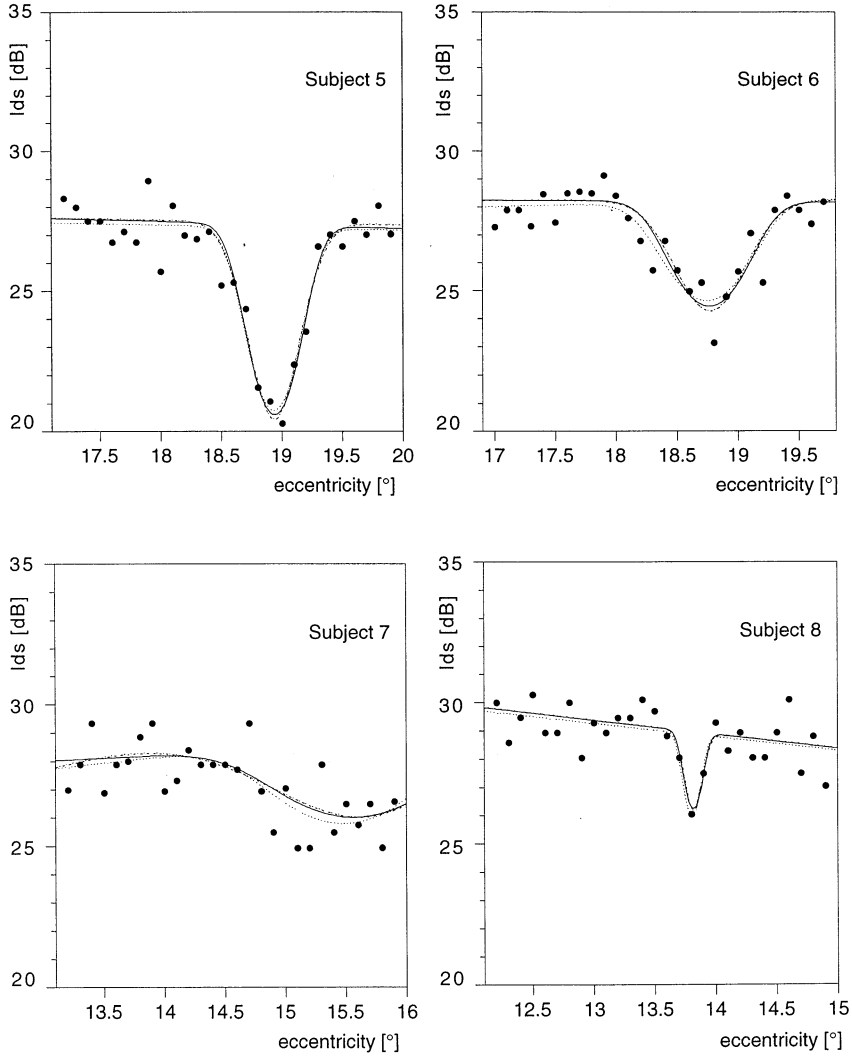

Fig. 3. (*Continued*)

stimulus with intensity x_{ij} and given at location ϕ_j can be described as

$$\Pr(Y_{ij}=1)=\frac{1}{1+\exp\left(\frac{\mu_\theta(\phi_j)-x_{ij}}{\sigma}\right)}, \quad (5)$$

where σ is the spread parameter which characterizes subjects uncertainty. Obviously $\Pr(Y_{ij}=0)=1-\Pr(Y_{ij}=1)$. Formula (5) is based on a common model for the psychometric function. In addition, it includes the relationship between threshold and location, considering all test points simultaneously.

The unknown parameters $\theta=(a, b, h, c, \delta)$ and σ can be estimated directly by maximum likelihood, i.e. by maximizing the log likelihood

$$\sum_{j=1}^{k}\sum_{i=1}^{n_j}\log\Pr(Y_{ij}=y_{ij}), \quad (6)$$

where y_{ij} is the realized response corresponding to x_{ij} and ϕ_j. This might be slightly more complex than two-stage fitting. However, it remains feasible with the help of good statistical packages, if the number of binary observations is not too small. We used the statistical software JMP™ 3.1.6 (SAS Institute Inc., Cary, NC, USA) and GAUSS™ 3.2.9 (Aptech Systems Inc., Maple Valley, WA, USA).

One-stage fitting renders an overall estimate of the spread parameter σ, which can be regarded as a measure of overall 'noise', whereas spread estimates from single maximum likelihood threshold estimates are very unreliable due to the small sample sizes.

2.3. Subjects and psychophysical methods

A total of 13 eyes from 13 ophthalmologically normal subjects, aged 22–38 years (six females and seven males), were examined by the Tübingen Computer Campimeter (TCC) using bright stimuli (32′) on a video display unit (VDU) and the implemented 4-2-1 dB strategy with four reversals (see Wabbels, Schiefer,

Treutwein, Benda & Stercken-Sorrenti, 1995). Stimulus duration was about 200 ms. By means of fundus oriented perimetry, individual perimetric grids were created including a line of 24 test points spaced in 0.1° intervals crossing a large retinal vessel almost perpendicularly and corresponding to one meridian (see Schiefer et al., 1996). Distance ϕ was set equal to the eccentricity of the test point.

Stimuli were presented on a high-resolution true-colour VDU (CALIBRATOR, Barco Inc., Kippenheim). This 'stimulus monitor' was calibrated by a mobile luminance meter to achieve homogeneous luminance data of background and stimuli over the entire surface of the VDU. After calibration, maximal luminance of the monitor was about 68 cd m^{-2} and minimal was about 0.19 cd m^{-2}. A red diamond figure was electronically cross-faded in the center of the screen as a fixation target. Fixation was monitored either visually or with the help of an IR video camera attached to the chin and head rest sampling pupillary diameter and position every 40 ms using a special graphic board (see Schiefer et al., 1996).

lds was calculated after Flammer (1993), slightly modified by referring the absolute value of the luminance difference between actual stimulus and background ($|L|$) to a luminance of 1000 cd m^{-2}:

$$\text{lds(db)} = 10 \log\left(\frac{1000\ \text{cd m}^{-2}}{|L|}\right)$$

(see Wabbels et al., 1995 and Schiefer et al., 1996). The reference (baseline) value of 1000 cd m^{-2} was arbitrarily chosen. As such baseline values differ between various publications lds results will also be different between these studies. However, this fact is of minor importance as a logarithmic scale is used and therefore, there is only a linear shift in the data. As a consequence, the description of angioscotoma as related to the surrounding lds level remains comparable.

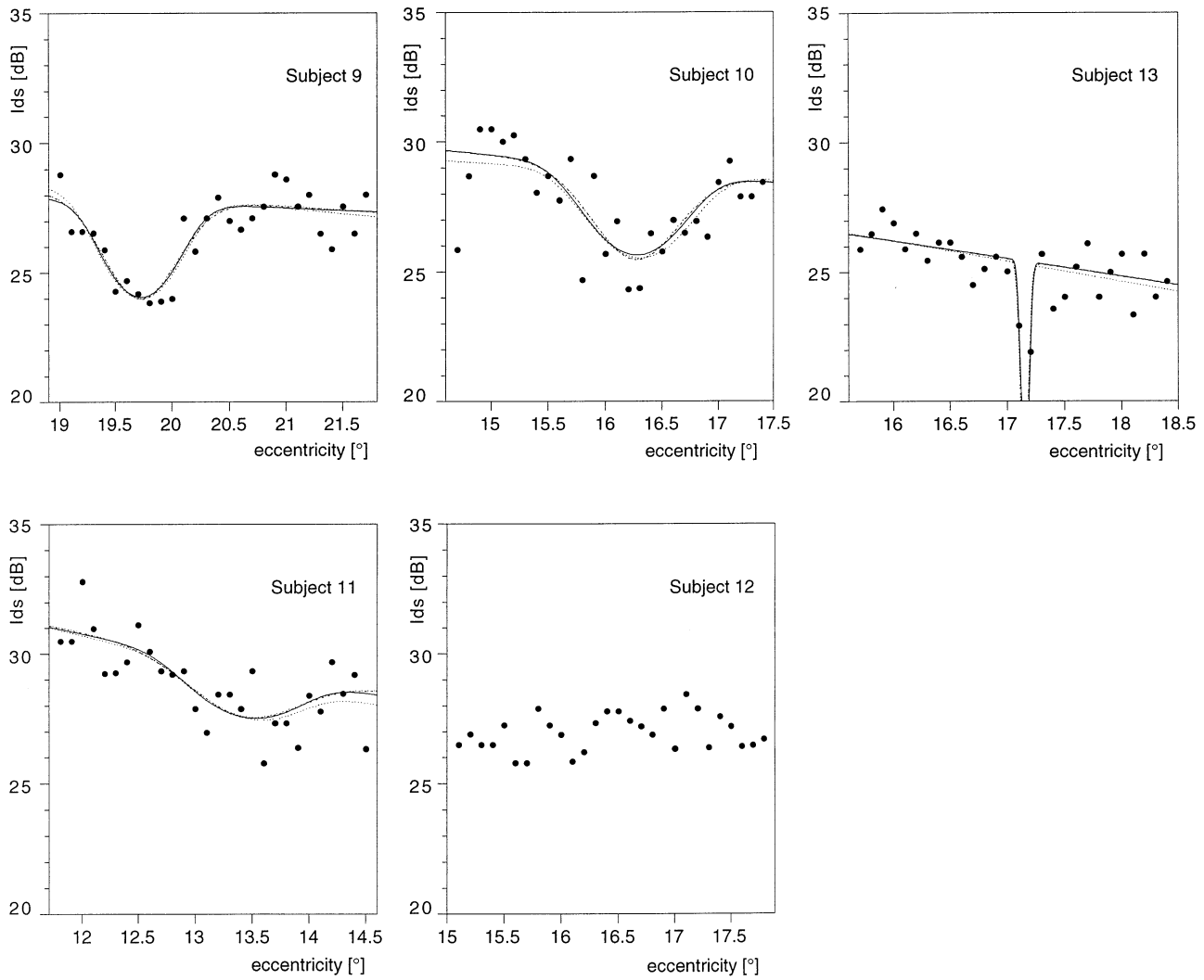

Fig. 3. (*Continued*)

Table 2
Estimated spread parameters for 12 ophthalmologically normal subjects using two different pararmetric functions for threshold course

Subject	tanh	Gaussian
1	0.94	0.96
2	0.76	0.76
3	0.91	0.91
4	1.00	0.99
5	0.76	0.75
6	0.76	0.74
7	0.85	0.84
8	0.62	0.63
9	0.80	0.80
10	1.15	1.14
11	0.87	0.88
13	0.93	0.93

Table 3
Mean maximum log likelihood for 12 ophthalmologically normal subjects using three different parametric functions for threshold course and number of stimulus presentations n

Subject	n	tanh	Gaussian	Linear
1	232	−0.4439	−0.4465	−0.5243
2	196	−0.4252	−0.4257	−0.4939
3	230	−0.4475	−0.4477	−-0.5091
4	222	−0.4368	−0.4367	−0.4787
5	244	−0.4016	−0.3992	−0.5697
6	219	−0.3973	−0.3949	−0.5015
7	230	−0.4116	−0.4121	−0.4226
8	208	−0.3955	−0.3960	−0.4322
9	234	−0.4077	−0.4075	−0.4813
10	223	−0.4478	−0.4463	−0.5051
11	201	−0.4389	−0.4408	−0.4737
13	217	−0.4626	−0.4626	−0.5124

Due to above mentioned procedure for the determination of lds values, the dB scale for bright stimuli was terminated by a maximal contrast of approximately 13 dB. (The exact value depending on stimulus location.)

3. Results

In 12 subjects, an angioscotoma was detected and a reasonable fit was achieved. One- and two-stage fitting methods, as well as the two different parametric functions (1) and (2) rendered very similar results. Only one subject (subject 12) did not show lowered lds. One- and two-stage angioscotoma width and depth estimations using parametrization (1) are given in Table 1. Fig. 3 shows the different threshold course estimations including one-stage fit using the Gaussian-like parametrization (2).

Table 2 gives the different spread estimates produced by one-stage fitting employing the two parametrizations, which yielded almost the same estimates. To compare the two parametric functions with respect to their goodness of fit, mean maximum log likelihood for each subject are given in Table 3. Higher maximum log likelihood indicates a better fit since both models use the same number of parameters. No preference can be seen, demonstrating similarity of both models.

In addition, Table 3 gives mean maximum log likelihood of one-stage fitting of a linear threshold course (3). Ignoring the fact that a sequential design (4-2-1 dB strategy) has been used, the presence of a scotoma would be tested by means of the corresponding likelihood ratio test. Twice the difference between the (whole) maximum log likelihood of the used parametrization and that of the linear fit was compared to the quantiles of a χ^2-distribution with three degrees of freedom. This would render a p-value of 0.17 in subject 7 and p-values less than 0.003 in all other subjects apart from subject 12.

Nevertheless, due to the sequentially constructed design, this gives only a rough idea. The construction of a correct test procedure for a sequentially collected sample remains a difficult theoretical task (see e.g. Silvey, 1980 pp. 66–67 and Morgan, 1992 p. 362).

On the other hand, a two-stage estimation avoids the problem of a sequentially constructed design since the used procedure is sequential only *within* the test location. A likelihood ratio test can be applied supposing a normal distribution of estimated thresholds. This leads to a p-value of 0.11 in subject 7, 0.03 in subject 11, and a p-values less than 0.002 in all other subjects apart from subject 12.

Hence, 11 subjects show a statistically significant scotoma using a significance level of 5%, ten subjects after adjusting for multiple testing, when two-stage fitting is employed.

In subject 13 a very sharp and small-sized scotoma was found. Estimation of scotoma depth is rather difficult since only two test points showed almost equally lowered lds. In this case, depth and width estimation are highly correlated and a better description would, in principle, demand an even denser perimetric grid. However, already small, physiological gaze movements are implicit limits of this procedure.

4. Discussion

From the theoretical point of view, one-stage fitting of angioscotomas, is preferable to a two-stage fitting, which handles single threshold estimates like homogeneous observations. A two-stage procedure dealing with single threshold estimates is easier to calculate. It often renders similar results and can be regarded as a simple approximation to one-stage fitting. However, only one-stage fitting renders an overall estimate for the spread parameter to measure threshold variability.

No differences were seen between the two proposed parametrization models for threshold course. Nevertheless, a better discrimination between different parametric functions requires a higher sample size.

In the case where the subject did not perceive any stimulus at one test location and no threshold can be estimated at this location, no reasonable two-stage fit can be achieved. Scotoma depth, especially, cannot be measured. The one-stage fitting method can still yield an estimate. However, it depends crucially on the supposed model. In such a case, only a good knowledge of angioscotoma shape would facilitate a confidential description.

Narrow scotoma can only be described sufficiently if a perimetric grid with adequate stimulus density is applied and interference factors (fixation instability) remain comparatively small. When only one or two test points indicate a lowering in lds, scotoma width and/or depth cannot be estimated precisely.

A general problem consists in an unstable fixation by the experimental subject. Fixation lapses, as well as inattention, can change single threshold estimates considerably, and, hence, the two-stage scotoma fitting curve. Instability of fixation on the one hand blurs angioscotoma borders (see e.g. Eizenman, Trope, Fortinsky & Murphy 1992; Schiefer et al., 1996). On the other hand, minimum eye movements, like tremor (10–15″), drifts (1–6′), as well as 'microsaccades' (Baumgartner, Bornschein, Hanitzsch, Jung, Kornhuber, Rentschler, Schober & Thoden, 1978) are physiological and essential for avoiding local adaptation and Troxler phenomenon. One-stage fitting should be much more robust against the occurrence of such lapses, due to a global estimate for the spread parameter. Nevertheless, in both models, a bad fixation can mask the effect caused by the retinal vessel. Hence, the description of small scotomas demands good fixation.

In three subjects unstable fixation seems to have blurred the effect of the supposed angioscotoma. In subject 12, no reasonable fit could be achieved at all. In subjects 7 and 11, definition of an angioscotoma is rather vague, which is, in subject 7, also indicated by a high p-value (0.11) of the likelihood ratio test to the hypothesis of no angioscotoma.

However, in most subjects reasonable estimates of angioscotoma width and depth, were found, although we evaluated only the data from one perimetric session for each subject. A combination of several examinations of the same subject, a video supervised fixation, as well as optimized procedures for stimulus presentation should improve the estimation.

We found (by one-stage fitting) angioscotoma widths of between 0.1 and 2°, and depths of between 1 and 8 dB, which agree with the findings made by Häberlin et al. (1983) which were already mentioned in the introduction. Supposing an unstable fixation, the measured scotoma would be rather deeper. This indicates that a visual field examination using bright stimuli, has to take into account the possibility of a reduction in lds of up to 10 dB caused by a retinal vessel.

5. Conclusions

Using a special perimetric grid, small scotoma can be described by several mathematical models. Fitting threshold estimates to a given parametric function of the threshold course renders results similar to a model which includes the threshold as a function of position into the probabilistic description of the binary response. However, only the latter model can give a confidential estimate of subjects' unsureness. In situations where the number of test points with a lowered lds is only one or two a scotoma can be detected but is difficult to describe, regardless of the used model.

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